KETORLAC TROMETHAMINE - ketorolac tromethamine tablet, film coated
TEVA PHARMACEUTICALS USA

WARNING

Ketorolac tromethamine, a non-steroidal anti-inflammatory drug (NSAID), is indicated for the short-term (up to 5 days) management of moderately severe, acute pain, that requires analgesia at the opioid level. It is NOT indicated for minor or chronic painful conditions. Ketorolac tromethamine is a potent NSAID analgesic, and its administration carries many risks. The resulting NSAID-related adverse events can be serious in certain patients for whom ketorolac tromethamine is indicated, especially when the drug is used inappropriately. Increasing the dose of ketorolac tromethamine beyond the label recommendations will not provide better efficacy but will result in increasing the risk of developing serious adverse events.

Cardiovascular Risk

- **NSAIDs[11] may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See WARNINGS.)**

- **Ketorolac tromethamine tablets are contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery. (See WARNINGS.)**

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1[1] Throughout this package insert, the term NSAID refers to a non-aspirin non-steroidal anti-inflammatory drug.

Gastrointestinal Risk

- **NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. (See WARNINGS.)**

Renal Effects

- **Ketorolac tromethamine is CONTRAINDICATED in patients with advanced renal impairment and in patients at risk for renal failure due to volume depletion (see WARNINGS).**

Risk of Bleeding

- **Ketorolac tromethamine inhibits platelet function and is, therefore, CONTRAINDICATED in patients with suspected or confirmed cerebrovascular bleeding, patients with hemorrhagic diathesis, incomplete hemostasis, and those at high risk of bleeding (see WARNINGS and PRECAUTIONS).**

- **Ketorolac tromethamine is CONTRAINDICATED as prophylactic analgesic before any major surgery, and is CONTRAINDICATED intra-operatively when hemostasis is critical because of the increased risk of bleeding.**

Hypersensitivity

- **Hypersensitivity reactions, ranging from bronchospasm to anaphylactic shock, have occurred and appropriate counteractive measures must be available when administering the first dose of ketorolac tromethamine-I.V./I.M. (see CONTRAINDICATIONS and WARNINGS). It is CONTRAINDICATED in patients with previously demonstrated hypersensitivity to ketorolac tromethamine, or allergic manifestations to aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs).**

Labor, Delivery, and Nursing

- **The use of ketorolac tromethamine in labor and delivery is CONTRAINDICATED because it may adversely affect fetal circulation and inhibit uterine contractions.**

- **The use of ketorolac tromethamine is CONTRAINDICATED in nursing mothers because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates.**

Concomitant Use with NSAIDs

- **Ketorolac tromethamine is CONTRAINDICATED in patients currently receiving ASA or NSAIDs because of the cumulative risk of inducing serious NSAID-related side effects.**

Dosage and Administration

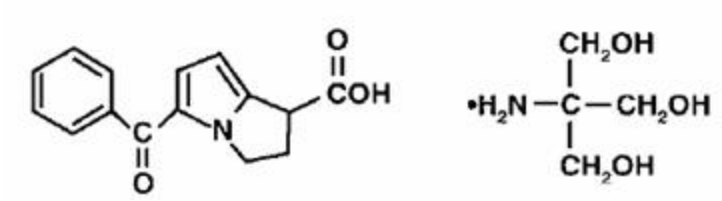
Ketorlac Tromethamine Tablets

- **Ketorolac tromethamine tablets are indicated only as continuation therapy to ketorolac tromethamine-I.V./I.M., and the combined duration of use of ketorolac tromethamine-I.V./I.M. and ketorolac tromethamine tablets is not to exceed 5 (five) days, because of the increased risk of serious adverse events.**

- **The recommended totally daily dose of ketorolac tromethamine tablets (maximum 40 mg) is significantly lower than for ketorolac tromethamine-I.V./I.M. (maximum 120 mg) (see DOSAGE AND ADMINISTRATION and Transition from Ketorolac Tromethamine-I.V./I.M. to Ketorolac Tromethamine Tablets).**

DESCRIPTION

Ketorolac tromethamine is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs). The chemical name for ketorolac tromethamine is (±)-5-benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol. The structural formula is:



$C_{19}H_{24}N_2O_6$ M.W. 376.41

Ketorolac tromethamine is a racemic mixture of [-]S and [+]R ketorolac tromethamine. Ketorolac tromethamine may exist in three crystal forms. All forms are equally soluble in water. Ketorolac tromethamine has a pKa of 3.5 and an n-octanol/water partition coefficient of 0.26.

Each tablet, for oral administration, contains 10 mg ketorolac tromethamine. In addition, each tablet contains the following inactive ingredients: hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug (NSAID). Ketorolac tromethamine inhibits synthesis of prostaglandins and may be considered a peripherally acting analgesic. The biological activity of ketorolac tromethamine is associated with the S-form. Ketorolac tromethamine possesses no sedative or anxiolytic properties.

Pain relief was statistically different after ketorolac tromethamine dosing from that of placebo at 1/2 hour (the first time point at which it was measured) following the largest recommended doses of ketorolac tromethamine, and by 1 hour following the smallest recommended doses. The peak analgesic effect occurred within 2 to 3 hours and was not statistically significantly different over the recommended dosage range of ketorolac tromethamine. The greatest difference between large and small doses of ketorolac tromethamine by either route was in the duration of analgesia.

Pharmacokinetics

Ketorolac tromethamine is a racemic mixture of [-]S- and [+]R-enantiomeric forms, with the S-form having analgesic activity.

Comparison of I.V., I.M., and Oral Pharmacokinetics

The pharmacokinetics of ketorolac tromethamine following I.V., I.M., and oral doses of ketorolac tromethamine, are compared in **TABLE 1**. The extent of bioavailability following administration of the oral and I.M. forms of ketorolac tromethamine was equal to that following an I.V. bolus.

Linear Kinetics

Following administration of single oral, I.M., or I.V. doses of ketorolac tromethamine, in the recommended dosage ranges, the clearance of the racemate does not change. This implies that the pharmacokinetics of ketorolac tromethamine in humans, following single or multiple I.M., I.V., or recommended oral doses of ketorolac tromethamine, are linear. At the higher recommended doses, there is a proportional increase in the concentrations of free and bound racemate.

Binding and Distribution

The ketorolac tromethamine racemate has been shown to be highly protein-bound (99%). Nevertheless, even plasma concentrations as high as 10 mcg/mL will only occupy approximately 5% of the albumin binding sites. Thus, the unbound fraction for each enantiomer will be constant over the therapeutic range. A decrease in serum albumin, however, will result in increased free drug concentrations.

The mean apparent volume ($V_ß$) of ketorolac tromethamine following complete distribution was approximately 13 liters. This parameter was determined from single dose data.

Metabolism

Ketorolac tromethamine is largely metabolized in the liver. The metabolic products are hydroxylated and conjugated forms of the parent drug. The products of metabolism, and some unchanged drug, are excreted in the urine.

Clearance and Excretion

A single-dose study with 10 mg ketorolac tromethamine (n = 9) demonstrated that the S-enantiomer is cleared approximately two times faster than the R-enantiomer, and that the clearance was independent of the route of administration. This means that the ratio of S/R plasma concentrations decreases with time after each dose. There is little or no inversion of the R- to S- form in humans.

The clearance of the racemate in normal subjects, elderly individuals, and in hepatically and renally impaired patients, is outlined in **TABLE 2**.

The half-life of the ketorolac tromethamine S-enantiomer was approximately 2.5 hours (SD ± 0.4) compared with 5 hours (SD ± 1.7) for the R-enantiomer. In other studies, the half-life for the racemate has been reported to lie within the range of 5 to 6 hours.

Accumulation
Ketorolac tromethamine administered as an I.V. bolus, every 6 hours, for 5 days, to healthy subjects (n = 13), showed no significant difference in C_{max} on Day 1 and Day 5. Trough levels averaged 0.29 mcg/mL (SD ± 0.13) on Day 1 and 0.55 mcg/mL (SD ± 0.23) on Day 6. Steady-state was approached after the fourth dose.

Accumulation of ketorolac tromethamine has not been studied in special populations (elderly patients, renal failure patients, or hepatic disease patients).

Effects of Food
Oral administration of ketorolac tromethamine tablets after a high fat meal resulted in decreased peak and delayed time-to-peak concentrations of ketorolac tromethamine by about 1 hour. Antacids did not affect the extent of absorption.

Kinetics in Special Populations

Elderly Patients
Based on single-dose data only, the half-life of the ketorolac tromethamine racemate increased from 5 to 7 hours in the elderly (65 to 78 years) compared with young healthy volunteers (24 to 35 years) (see **TABLE 2**). There was little difference in the C_{max} for the two groups (elderly, 2.52 mcg/mL ± 0.77; young, 2.99 mcg/mL ± 1.03) (see **PRECAUTIONS**, **Geriatric Use**).

Renally Impaired Patients
Based on single-dose data only, the mean half-life of ketorolac tromethamine in renally impaired patients is between 6 and 19 hours, and is dependent on the extent of the impairment. There is poor correlation between creatinine clearance and total ketorolac tromethamine clearance in the elderly and populations with renal impairment (r = 0.5).

In patients with renal disease, the AUC of each enantiomer increased by approximately 100% compared with healthy volunteers. The volume of distribution doubles for the S-enantiomer and increases by 1/5th for the R-enantiomer. The increase in volume of distribution of ketorolac tromethamine implies an increase in unbound fraction.

The AUC -ratio of the ketorolac tromethamine enantiomers in healthy subjects and patients remained similar, indicating there was no selective excretion of either enantiomer in patients compared to healthy subjects (see **WARNINGS**, **Renal Effects**).

Hepatic Effects
There was no significant difference in estimates of half-life, AUC, C_{max}, in 7 patients with liver disease compared to healthy volunteers (see **PRECAUTIONS**, **Hepatic Effects**).

TABLE 1: Table of Approximate Average Pharmacokinetic Parameters (Mean ± SD) Following Oral, Intramuscular and Intravenous Doses of Ketorolac Tromethamine

Pharmacokinetic Parameters (units)	**Oral**[+2]	**Intramuscular**[§3]			**Intravenous Bolus**[*4]	
	10 mg	**15 mg**	**30 mg**	**60 mg**	**15 mg**	**30 mg**
Bioavailability (extent)	100%					
T_{max}[17](min)	44 ± 34	33 ± 21[**5]	44 ± 29	33 ± 21[**5]	1.1 ± 0.7[**5]	2.9 ± 1.8
C_{max}[28](mcg/mL) [single-dose]	0.87 ± 0.22	1.14 ± 0.32[**5]	2.42 ± 0.68	4.55 ± 1.27[**5]	2.47 ± 0.51[**5]	4.65 ± 0.96
C_{max} (mcg/mL) [steady state q.i.d.]	1.05 ± 0.26[**5]	1.56 ± 0.44[**5]	3.11 ± 0.87[**5]	N/A[++6]	3.09 ± 1.17[**5]	6.85 ± 2.61
C_{min}[39](mcg/mL) [steady state q.i.d.]	0.29 ± 0.07[**5]	0.47 ± 0.13[**5]	0.93 ± 0.26[**5]	N/A	0.61 ± 0.21[**5]	1.04 ± 0.35

C_{ave}[410](mcg/mL) [steady state q.i.d.]	0.59 ± 0.2[**5]	0.94 ± 0.29[**5]	1.88 ± 0.59[**5]	N/A	1.09 ± 0.3[**5]	2.17 ± 0.59
$V_{ß}$[511](L/kg)	0.175 ± 0.039				0.21 ± 0.044	

% Dose metabolized ≤ 50 % Dose excreted in feces = 6

% Dose excreted in urine = 91 % Plasma protein binding = 99

TABLE 2: The Influence of Age, Liver and Kidney Function, on the Clearance and Terminal Half-Life of Ketorolac Tromethamine (I.M.[112] and Oral[213])

	Total Clearance [in L/h/kg][314]		**Terminal Half-life [in hours]**	
Types of Subjects	**I.M. Mean (range)**	**ORAL Mean (range)**	**I.M. Mean (range)**	**ORAL Mean (range)**
Normal Subjects I.M. (n = 54) mean age = 32, range = 18 to 60 Oral (n = 77) mean age = 32, range = 20 to 60	0.023 (0.01 to 0.046)	0.025 (0.013 to 0.05)	5.3 (3.5 to 9.2)	5.3 (2.4 to 9)
Healthy Elderly Subjects I.M.(n = 13), Oral (n = 12) mean age = 72, range = 65 to 78	0.019 (0.013 to 0.034)	0.024 (0.018 to 0.034)	7 (4.7 to 8.6)	6.1 (4.3 to 7.6)
Patients with Hepatic Dysfunction I.M. and Oral (n = 7) mean age = 51, range = 43 to 64	0.029 (0.013 to 0.066)	0.033 (0.019 to 0.051)	5.4 (2.2 to 6.9)	4.5 (1.6 to 7.6)
Patients with Renal Impairment I.M.(n = 25), Oral (n = 9) serum creatinine = 1.9 to 5 mg/dL, mean age (I.M.) = 54, range = 35 to 71 mean age (oral) = 57, range = 39 to 70	0.015 (0.005 to 0.043)	0.016 (0.007 to 0.052)	10.3 (5.9 to 19.2)	10.8 (3.4 to 18.9)
Renal Dialysis Patients I.M. and Oral (n = 9), mean age = 40, range = 27 to 63	0.016 (0.003 to 0.036)	--	13.6 (8 to 39.1)	--

I.V. Administration: In normal subjects (n = 37), the total clearance of 30 mg I.V. administered ketorolac tromethamine was 0.03 (0.017 to 0.051) L/h/kg. The terminal half-life was 5.6 (4 to 7.9) hours.

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2[+] Derived from P.O. pharmacokinetic studies in 77 normal fasted volunteers

3[§] Derived from I.M.pharmacokinetic studies in 54 normal volunteers

4[*] Derived from I.V. pharmacokinetic studies in 24 normal volunteers

5[**] Mean value was simulated from observed plasma concentration data and standard deviation was simulated from percent coefficient of variation for observed Cmax and Tmax data

6[++] Not Applicable because 60 mg is only recommended as a single-dose

7[1] Time-to-peak plasma concentration

8[2] Peak plasma concentration

9[3] Trough plasma concentration

10[4] Average plasma concentration

11[5] Volume of Distribution

12[1] Estimated from 30 mg single I.M. doses of ketorolac tromethamine

13[2] Estimated from 10 mg single oral doses of ketorolac tromethamine

14[3] Liters/hour/kilogram

Clinical Studies

The analgesic efficacy of intramuscularly, intravenously and orally administered ketorolac tromethamine was investigated in two postoperative pain models: general surgery (orthopedic, gynecologic and abdominal) and oral surgery (removal of impacted third molars). The studies were double-blind, single- and multiple-dose, parallel trial designs, in patients with moderate to severe pain at baseline. Ketorolac tromethamine-I.V./I.M. was compared as follows: I.M. to meperidine or morphine administered intramuscularly, and I.V. to morphine administered either directly I.V. or through a PCA (Patient-Controlled Analgesia) pump.

Short-Term Use (up to 5 days) Studies

In the comparisons of intramuscular administration during the first hour, the onset of analgesic action was similar for ketorolac tromethamine and the narcotics, but the duration of analgesia was longer with ketorolac tromethamine than with the opioid comparators meperidine or morphine.

In a multi-dose, postoperative (general surgery) double-blind trial of ketorolac tromethamine-I.M.30 mg versus morphine 6 and 12 mg I.M., each drug given on an "as needed" basis for up to 5 days, the overall analgesic effect of ketorolac tromethamine-I.M. 30 mg was between that of morphine 6 and 12 mg. The majority of patients treated with either ketorolac tromethamine or morphine were dosed for up to 3 days; a small percentage of patients received 5 days of dosing.

In clinical settings where perioperative morphine was allowed, ketorolac tromethamine-I.V. 30 mg, given once or twice as needed, provided analgesia comparable to morphine 4 mg I.V. once or twice as needed.

There was relatively limited experience with 5 consecutive days of ketorolac tromethamine-I.V. use in controlled clinical trials, as most patients were given the drug for 3 days or less. The adverse events seen with I.V.-administered ketorolac tromethamine were similar to those observed with I.M.-administered ketorolac tromethamine, as would be expected based on the similar pharmacokinetics and bioequivalence (AUC, clearance, plasma half-life) of I.V. and I.M. routes of ketorolac tromethamine administration.

Clinical Studies with Concomitant Use of Opioids

Clinical studies in postoperative pain management have demonstrated that ketorolac tromethamine-I.V./I.M., when used in combination with opioids, significantly reduced opioid consumption. This combination may be useful in the subpopulation of patients especially prone to opioid-related complications. Ketorolac tromethamine and narcotics should not be administered in the same syringe.

In a postoperative study, where all patients received morphine by a PCA device, patients treated with ketorolac tromethamine-I.V. as fixed intermittent boluses (e.g., 30 mg initial dose followed by 15 mg q3h), required significantly less morphine (26%) than the placebo group. Analgesia was significantly superior, at various postdosing pain assessment times, in the patients receiving ketorolac tromethamine-I.V. plus PCA morphine as compared to patients receiving PCA-administered morphine alone.

Postmarketing Surveillance Study

A large postmarketing observational, non-randomized study, involving approximately 10,000 patients receiving ketorolac tromethamine, demonstrated that the risk of clinically serious gastrointestinal (G.I.) bleeding was dose-dependent (see **TABLE 3A** and **3B**). This was particularly true in elderly patients who received an average daily dose greater than 60 mg/day of ketorolac tromethamine (**TABLE 3A**).

TABLE 3: Incidence of Clinically Serious G.I. Bleeding as Related to Age, Total Daily Dose, and History of G.I. Perforation, Ulcer, Bleeding (PUB) after up to 5 Days of Treatment with Ketorolac Tromethamine-I.V./I.M.

A. Patients without a History of PUB

Age of Patients	Total Daily Dose of Ketorolac Tromethamine-I.V./I.M.			
	≤ 60 mg	> 60 to 90 mg	> 90 to 120 mg	> 120 mg
< 65 years of age	0.4%	0.4%	0.9%	4.6%
≥ 65 years of age	1.2%	2.8%	2.2%	7.7%

B. Patients with History of PUB

Age of Patients	Total Daily Dose of Ketorolac Tromethamine-I.V./I.M.			
	≤ 60 mg	> 60 to 90 mg	> 90 to 120 mg	> 120 mg
< 65 years of age	0.4%	0.4%	0.9%	4.6%

≥ 65 years of age	1.2%	2.8%	2.2%	7.7%

INDICATIONS AND USAGE

Carefully consider the potential benefits and risks of ketorolac tromethamine tablets and other treatment options before deciding to use ketorolac tromethamine tablets. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).

Ketorolac tromethamine is indicated for the short-term (≤ 5 days) management of moderately severe, acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Therapy should always be initiated with ketorolac tromethamine-I.V./.IM., and ketorolac tromethamine tablets are to be used only as continuation treatment, if necessary. Combined use of ketorolac tromethamine-I.V./I.M. and ketorolac tromethamine tablets is not to exceed 5 days of use because of the potential of increasing the frequency and severity of adverse reactions associated with the recommended doses (see **WARNINGS**, **PRECAUTIONS**, **DOSAGE AND ADMINISTRATION**, and **ADVERSE REACTIONS**). Patients should be switched to alternative analgesics as soon as possible, but ketorolac tromethamine therapy is not to exceed 5 days.

CONTRAINDICATIONS (SEE ALSO BOXED WARNING)

Ketorolac tromethamine tablets are contraindicated in patients with known hypersensitivity to ketorolac.

Ketorolac tromethamine tablets should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see **WARNINGS**, **Anaphylactoid Reactions** and **PRECAUTIONS**, **Preexisting Asthma**).

Ketorolac tromethamine tablets are contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

- Ketorolac tromethamine is CONTRAINDICATED in patients with active peptic ulcer disease, in patients with recent gastrointestinal bleeding or perforation, and in patients with a history of peptic ulcer disease or gastrointestinal bleeding.
- Ketorolac tromethamine is CONTRAINDICATED in patients with advanced renal impairment, or in patients at risk for renal failure due to volume depletion (see WARNINGS for correction of volume depletion).
- Ketorolac tromethamine is CONTRAINDICATED in labor and delivery because, through its prostaglandin synthesis inhibitory effect, it may adversely affect fetal circulation and inhibit uterine musculature, thus increasing the risk of uterine hemorrhage.
- The use of ketorolac tromethamine is CONTRAINDICATED in nursing mothers because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates.
- Ketorolac tromethamine is CONTRAINDICATED as prophylactic analgesic before any major surgery, and is CONTRAINDICATED intra-operatively when hemostasis is critical because of the increased risk of bleeding.
- Ketorolac tromethamine inhibits platelet function and is, therefore, CONTRAINDICATED in patients with suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis, and those at high risk of bleeding (see **WARNINGS** and **PRECAUTIONS**).
- Ketorolac tromethamine is CONTRAINDICATED in patients currently receiving ASA or NSAIDs because of the cumulative risks of inducing serious NSAID related adverse events.
- The concomitant use of ketorolac tromethamine and probenecid is CONTRAINDICATED.

WARNINGS (SEE ALSO BOXED WARNING)

Cardiovascular Effects

Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (see **GI WARNINGS**).

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10 to 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see **CONTRAINDICATIONS**).

Hypertension
NSAIDs, including ketorolac tromethamine tablets, can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including ketorolac tromethamine tablets, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Edema
Fluid retention and edema have been observed in some patients taking NSAIDs. Ketorolac tromethamine tablets should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal Effects – Risk of Ulceration, Bleeding, and Perforation
NSAIDs, including ketorolac tromethamine tablets, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3 to 6 months, and in about 2 to 4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.
NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* who use NSAIDs have a greater than 10 fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.
To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Renal Effects
Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Advanced Renal Disease
No information is available from controlled clinical studies regarding the use of ketorolac tromethamine tablets in patients with advanced renal disease. Therefore, treatment with ketorolac tromethamine tablets is not recommended in these patients with advanced renal disease. If Ketorolac tromethamine tablet therapy must be initiated, close monitoring of the patient's renal function is advisable.

Anaphylactoid Reactions
As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to ketorolac tromethamine tablets. Ketorolac tromethamine tablets should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see **CONTRAINDICATIONS** and **PRECAUTIONS**, **Preexisting Asthma**). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin Reactions
NSAIDs, including ketorolac tromethamine tablets, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy
In late pregnancy, as with other NSAIDs, ketorolac tromethamine tablets should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General
Ketorolac tromethamine tablets cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.
The pharmacological activity of ketorolac tromethamine tablets in reducing inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

Hepatic Effects
Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including ketorolac tromethamine tablets. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.
A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with ketorolac tromethamine tablets. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), ketorolac tromethamine tablets should be discontinued.

Hematological Effects
Anemia is sometimes seen in patients receiving NSAIDs, including ketorolac tromethamine tablets. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including ketorolac tromethamine tablets, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.
NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving ketorolac tromethamine tablets who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Preexisting Asthma
Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, ketorolac tromethamine tablets should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Information for Patients
Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy. Patients should also be encouraged to read the NSAID Medication Guide that accompanies each prescription dispensed.

1. Ketorolac tromethamine tablets, like other NSAIDs, may cause serious CV side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up (see **WARNINGS, Cardiovascular Effects**).

2. Ketorolac tromethamine tablets, like other NSAIDs, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up (see **WARNINGS, Gastrointestinal Effects - Risk of Ulceration, Bleeding, and Perforation**).

3. Ketorolac tromethamine tablets, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and

should ask for medical advice when observing any indicative signs or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.

4. Patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians.

5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

6. Patients should be informed of the signs of an anaphylactoid reaction (e.g. difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help (see **WARNINGS**).

7. In late pregnancy, as with other NSAIDs, ketorolac tromethamine tablets should be avoided because it will cause premature closure of the ductus arteriosus.

Laboratory Tests
Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs, should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, ketorolac tromethamine tablets should be discontinued.

Drug Interactions

ACE-inhibitors
Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

Aspirin
When ketorolac tromethamine tablets are administered with aspirin, its protein binding is reduced, although the clearance of free ketorolac is not altered. The clinical significance of this interaction is not known, however, as with other NSAIDs, concomitant administration of ketorolac tromethamine tablets and aspirin is not generally recommended because of the potential of increased adverse effects.

Furosemide
Clinical studies, as well as post marketing observations, have shown that ketorolac tromethamine tablets can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure (see **WARNINGS**, **Renal Effects**), as well as to assure diuretic efficacy.

Lithium
NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate
NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Warfarin
The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

Carcinogenesis, Mutagenesis, Impairment of Fertility
An 18 month study in mice with oral doses of ketorolac tromethamine at 2 mg/kg/day (0.9 times the human systemic exposure at the recommended I.M. or I.V. dose of 30 mg q.i.d., based on area-under-the-plasma-concentration curve [AUC]), and a 24 month study in rats at 5 mg/kg/day (0.5 times the human AUC), showed no evidence of tumorigenicity.
Ketorolac tromethamine was not mutagenic in the Ames test, unscheduled DNA synthesis and repair, and in forward mutation assays. Ketorolac tromethamine did not cause chromosome breakage in the *in vivo* mouse micronucleus assay. At 1590 mcg/mL and at higher concentrations, ketorolac tromethamine increased the incidence of chromosomal aberrations in Chinese hamster ovarian cells.
Impairment of fertility did not occur in male or female rats at oral doses of 9 mg/kg (0.9 times the human AUC) and 16 mg/kg (1.6 times the human AUC) of ketorolac tromethamine, respectively.

Pregnancy

Teratogenic Effects

Pregnancy category C
Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women.

Nonteratogenic Effects
Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of the ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

Labor and Delivery
In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of ketorolac tromethamine tablets on labor and delivery in pregnant women are unknown.

Nursing Mothers
After a single administration of 10 mg of ketorolac tromethamine tablets to humans, the maximum milk concentration observed was 7.3 ng/mL and the maximum milk-to-plasma ratio was 0.037. After one day of dosing (q.i.d.), the maximum milk concentration was 7.9 ng/mL and the maximum milk-to-plasma ratio was 0.025. Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers is contraindicated.

Pediatric Use
Safety and efficacy in pediatric patients (less than 16 years of age) have not been established.

Geriatric Use
As with any NSAIDs, caution should be exercised in treating the elderly (65 years and older).

ADVERSE REACTIONS
Adverse reaction rates increase with higher doses of ketorolac tromethamine. Practitioners should be alert for the severe complications of treatment with ketorolac tromethamine, such as G.I. ulceration, bleeding and perforation, postoperative bleeding, acute renal failure, anaphylactic and anaphylactoid reactions, and liver failure (see **Boxed WARNING**, **WARNINGS**, **PRECAUTIONS**, and **DOSAGE AND ADMINISTRATION**). These NSAID-related complications can be serious in certain patients for whom ketorolac tromethamine is indicated, especially when the drug is used inappropriately.
The adverse reactions listed below were reported in clinical trials as probably related to ketorolac tromethamine.
INCIDENCE GREATER THAN 1%
[Percentage of incidence in parentheses for those events reported in 3% or more patients]
Body as a Whole: edema (4%).
Cardiovascular: hypertension.
Dermatologic: pruritus, rash.
Gastrointestinal: nausea (12%), dyspepsia (12%), gastrointestinal pain (13%), diarrhea (7%), constipation, flatulence, gastrointestinal fullness, vomiting, stomatitis.
Hemic and Lymphatic: purpura.
Nervous System: headache (17%), drowsiness (6%), dizziness (7%), sweating.
INCIDENCE 1% OR LESS
Body as a Whole: weight gain, fever, infections, asthenia.
Cardiovascular: palpitation, pallor, syncope.
Dermatologic: urticaria.
Gastrointestinal: gastritis, rectal bleeding, eructation, anorexia, increased appetite.
Hemic and Lymphatic: epistaxis, anemia, eosinophilia.
Nervous System: tremors, abnormal dreams, hallucinations, euphoria, extrapyramidal symptoms, vertigo, paresthesia, depression, insomnia, nervousness, excessive thirst, dry mouth, abnormal thinking, inability to concentrate, hyperkinesis, stupor.
Respiratory: dyspnea, pulmonary edema, rhinitis, cough.
Special Senses: abnormal taste, abnormal vision, blurred vision, tinnitus, hearing loss.
Urogenital: hematuria, proteinuria, oliguria, urinary retention, polyuria, increased urinary frequency.
The following adverse events were reported from postmarketing experience.
Body as a Whole: hypersensitivity reactions such as anaphylaxis, anaphylactoid reaction, laryngeal edema, tongue edema (see **Boxed WARNING**, **WARNINGS**), myalgia.
Cardiovascular: hypotension and flushing.

Dermatologic: Lyell's syndrome, Stevens-Johnson syndrome, exfoliative dermatitis, maculo-papular rash, urticaria.
Gastrointestinal: peptic ulceration, GI hemorrhage, GI perforation (see **Boxed WARNING**, **WARNINGS**), melena, acute pancreatitis.
Hemic and Lymphatic: postoperative wound hemorrhage, rarely requiring blood transfusion (see **Boxed WARNING**, **WARNINGS**, and **PRECAUTIONS**), thrombocytopenia, leukopenia.
Hepatic: hepatitis, liver failure, cholestatic jaundice.
Nervous System: convulsions, psychosis, aseptic meningitis.
Respiratory: asthma, bronchospasm.
Urogenital: acute renal failure (see **Boxed WARNING**, **WARNINGS**), flank pain with or without hematuria and/or azotemia, nephritis, hyponatremia, hyperkalemia, hemolytic uremic syndrome.

OVERDOSAGE

In controlled overdosage, daily doses of 360 mg of ketorolac tromethamine-I.V./I.M. given for five days (3 times the highest recommended dose), caused abdominal pain and peptic ulcers which healed after discontinuation of dosing. Metabolic acidosis has been reported following intentional overdosage.
Dialysis does not significantly clear ketorolac tromethamine from the blood stream.

DOSAGE AND ADMINISTRATION

Carefully consider the potential benefits and risks of ketorolac tromethamine tablets and other treatment options before deciding to use ketorolac tromethamine tablets. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).
After observing the response to initial therapy with ketorolac tromethamine tablets, the dose and frequency should be adjusted to suit an individual patient's needs.
THE COMBINED DURATION OF USE OF KETOROLAC TROMETHAMINE-I.V./I.M. AND KETOROLAC TROMETHAMINE TABLETS IS NOT TO EXCEED FIVE (5) DAYS. THE USE OF KETOROLAC TROMETHAMINE TABLETS IS ONLY INDICATED AS CONTINUATION THERAPY TO KETOROLAC TROMETHAMINE-I.V./I.M..
Ketorolac tromethamine-I.V./I.M. may be used as a single, or multiple dose, on a regular or "prn" schedule for the management of moderately severe, acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Hypovolemia should be corrected prior to the administration of ketorolac tromethamine (see **WARNINGS**, Renal Effects). Patients should be switched to alternative analgesics as soon as possible, but ketorolac tromethamine therapy is not to exceed 5 days.
Ketorolac tromethamine tablets are indicated ONLY as continuation therapy to ketorolac tromethamine-I.V./I.M. for the management of moderately severe, acute pain that requires analgesia at the opioid level. See also **PRECAUTIONS**, **Information for Patients**.

Transition from Ketorolac Tromethamine-I.V./I.M. to Ketorolac Tromethamine Tablets

The recommended ketorolac tromethamine tablets dose is as follows:
• Patients < 65 years of age:

Two (2) tablets as a first oral dose for patients who received **60 mg I.M. single dose, 30 mg I.V. single dose or 30 mg multiple dose** ketorolac tromethamine-I.V./I.M. followed by one (1) tablet every 4 to 6 hours, not to exceed 40 mg/24 h of ketorolac tromethamine tablets.
• Patients ≥ 65 years of age, renally impaired and/or less than 50 kg (110 lbs.) of body weight:

One (1) tablet as a first oral dose for patients who received **30 mg I.M. single dose, 15 mg I.V. single dose or 15 mg multiple dose** ketorolac tromethamine-I.V./I.M. followed by one (1) tablet every 4 to 6 hours, not to exceed 40 mg/24 h of ketorolac tromethamine tablets.
Shortening the recommended dosing intervals may result in increased frequency and severity of adverse reactions.
The maximum combined duration of use (parenteral and oral ketorolac tromethamine) is limited to 5 days.

HOW SUPPLIED

Ketorolac tromethamine tablets USP, 10 mg are round, white, unscored, film-coated tablets debossed "93" on one side and "314" on the other side, available in bottles of 100.
Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

MEDICATION GUIDE FOR NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

(See the end of this Medication Guide for a list of prescription NSAID medicines.)
What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?
NSAID medicines may increase the chance of a heart attack or stroke that can lead to death. This chance increases:
• with longer use of NSAID medicines

• in people who have heart disease

NSAID medicines should never be used right before or after a heart surgery called a "coronary artery bypass graft (CABG." NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:
• can happen without warning symptoms

• may cause death

The chance of a person getting an ulcer or bleeding increases with:
• taking medicines called “corticosteroids” and “anticoagulants”

• longer use

• smoking

• drinking alcohol

• older age

• having poor health

NSAID medicines should only be used:
• exactly as prescribed

• at the lowest dose possible for your treatment

• for the shortest time needed

What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?
NSAID medicines are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as:
• different types of arthritis

• menstrual cramps and other types of short-term pain

Who should not take a Non-Steroidal Anti-Inflammatory Drug (NSAID)?
Do not take an NSAID medicine:
• if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine

• for pain right before or after heart bypass surgery

Tell your healthcare provider:
• about all of your medical conditions

• about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Keep a list of your medicines to show to your healthcare provider and pharmacist.**

• if you are pregnant. **NSAID medicines should not be used by pregnant women late in their pregnancy.**

• if you are breastfeeding. **Talk to your doctor.**

What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

Serious Side effects include:	**Other side effects include:**
• heart attack	• stomach pain
• stroke	• constipation
• high blood pressure	• diarrhea
• heart failure from body swelling (fluid retention)	• gas
	• heartburn
• kidney problems including kidney failure	• nausea
• bleeding and ulcers in the stomach and intestine	• vomiting
• low red blood cells (anemia)	• dizziness

• life-threatening skin reactions	
• life-threatening allergic reactions	
• liver problems including liver failure	
• asthma attacks in people who have asthma	

Get emergency help right away if you have any of the following symptoms:
- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms:
- nausea
- more tired or weaker than usual
- itching
- your skin or eyes look yellow
- stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms and legs, hands and feet

These are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

Other information about Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
- Aspirin is an NSAID medicine but it does not increase the chance of heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some of the NSAID medicines are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

NSAID medicines that need a prescription

Generic Name	**Tradename**
Celecoxib	Celebrex
Diclofenac	Cataflam, Voltaren, Arthrotec (combined with misoprostol)
Diflunisal	Dolobid
Etodolac	Lodine, Lodine XL
Fenoprofen	Nalfon, Nalfon 200
Flurbiprofen	Ansaid
Ibuprofen	Motrin, Tab-Profen, Vicoprofen (combined with hydrocodone), Combunox (combined with oxycodone)
Indomethacin	Indocin, Indocin SR, Indo-Lemmon, Indomethagan

Ketoprofen	Oruvail
Ketorolac	Toradol
Mefenamic Acid	Ponstel
Meloxicam	Mobic
Nabumetone	Relafen
Naproxen	Naprosyn, Anaprox, Anaprox DS, EC-Naproxyn, Naprelan, Naprapac (copackaged with lansoprazole)
Oxaprozin	Daypro
Piroxicam	Feldene
Sulindac	Clinoril
Tolmetin	Tolectin, Tolectin DS, Tolectin 600

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